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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Rajesh MANCHANDA et al.		Confirmation No.:	9728
Serial No.:	09/855,542	Examiner:	San Ming R. Hui
Filed:	May 16, 2001	Group Art Unit:	1617
Title:	STABILIZATION OF RADIONUCLIDE-CONTAINING COMPOSITIONS		

BRIEF ON APPEAL UNDER 37 C.F.R. § 41.37

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the decision of the Examiner finally rejecting claims 1-4, 6, 8-10 and 32-33 of the above-identified application.

(1) REAL PARTY IN INTEREST

The application is assigned of record to CIS bio international (Saclay, France), who is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 1-4, 6, 8-10 and 32-33, on appeal.
Claims allowed:	(None)
Claims canceled:	Claims 5, 15, 23-31 and 35.
Claims withdrawn:	Claims 7, 11-14, 16-22 and 34.
Claims on Appeal:	Claims 1-4, 6, 8-10 and 32-33 (Copy of claims on appeal in attached Appendix).

(4) STATUS OF AMENDMENTS

No amendments after the Final Rejection were proposed by Appellants.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' invention of claim 1, on appeal, is directed to a composition comprising:

- a radionuclide, excluding iodine radionuclides,
- a targeting agent, and
- iodide ions or a compound which releases or generates iodide ions

(see e.g., page 1, lines 3-13, page 4, second full paragraph, and original claim 1 of the instant specification). The iodide ions aid in stabilizing the composition against degradation thus maintaining high radiochemical purity of the composition (see, e.g., page 2, first paragraph under "Summary of the Invention" and original claim 1 of the instant specification). The targeting agent is a peptide, oligonucleotide, antibody or peptidomimetic, or is a targeting agent bonded to a complexing moiety, of the formula $A—CZ(B)—[C(R^1R^2)]_n—X$, wherein the variables are as defined in the claim 1 (see, e.g., page 3, lines 4-6, the paragraph bridging pages 3-4, and original claims 5 and 7 of the instant specification).

Appellants invention, of claim 32 on appeal, is directed to an embodiment of a composition within the scope of claim 1, on appeal. This composition comprises:

- a Tc-99m radionuclide,
- a depreotide or P2045 targeting agent, and
- iodide ions or a compound which releases or generates iodide ions,

where the iodide ions aid in stabilizing the composition against degradation thus maintaining high radiochemical purity of the composition (see, e.g., page 4, first and second full paragraphs, the Examples and original claims 9 and 10 of the instant specification).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The following outstanding grounds of rejection are requested to be reviewed on appeal. For each ground, any separate consideration of the claims subject to that rejection are indicated.

1. The rejection of claims 1-4, 6, 8-10 and 32-33, on appeal, under 35 U.S.C. §103, for allegedly being obvious over Solanki (U.S. Patent No. 5,262,175) in view of Cyr (U.S. Patent No. 6,881,396), is at issue in this appeal.

As to this rejection, claims 1, 4, 6, 8-10 and 32-33, on appeal, are grouped and argued together. Claims 2 and 3, on appeal, are separately grouped and argued for the reasons given in the argument.

(7) ARGUMENT

1a. Claims 1, 4, 6, 8-10 and 32-33 are not obvious to one of ordinary skill in the art from Solanki (U.S. Patent No. 5,262,175) in view of Cyr (U.S. Patent No. 6,881,396), and, thus, the rejection thereof under 35 U.S.C. §103 is not supported on the record.

Appellants urge that one of ordinary skill in the art would not have been motivated to combine the Solanki and Cyr teachings in the manner suggested in the Final Office Action, or otherwise, to render the invention of the claims on appeal obvious.

Solanki teaches a composition and method for stabilizing a radiopharmaceutical complex using a weak oxidizing agent. The complex to be stabilized in Solanki is a lipophilic complex containing a radionuclide, such as Tc-99m, and an organic complexing compound selected from propyleneamineoximes, mercaptoacetyl triglycines, bisaminothiols, kethoxal bisthiosemicarbazones and ethyl cysteinate dimers, or is a boronic acid adduct of these; see, e.g., col. 1, lines 7-30, and col. 2, lines 19-27, of Solanki. The weak oxidizing stabilizer taught by Solanki is specifically selected to stabilize this type of lipophilic complex with these type of complexing agents; see, e.g., col. 1, lines 65-68. See also, col. 3, lines 62-68, of Solanki describing that the instability is a result of these particular new types of neutral lipophilic complexes. Thus, Solanki teaches the use of the weak oxidizing agent as a stabilizer particularly in connection with radionuclides complexed with the specific propyleneamineoxime, mercaptoacetyl triglycine, bisaminothiol, kethoxal bisthiosemicarbazone and ethyl cysteinate dimer complexing agents.

Cyr teaches stabilizing a radiopharmaceutical by using a 6-hydroxychoman derivative as the stabilizer; see col. 1, lines 22-27. Although Cyr generally discloses that the agent may be used to stabilize peptide and non-peptide radiopharmaceuticals (col. 2, lines 35-39), there is particular emphasis on stabilizing radiopharmaceuticals having peptide-based targeting agents – all of the examples being directed thereto. See also col. 2, lines 18-20, indicating the particular need for stabilizers of radiopharmaceuticals containing peptide bonds. Further, Cyr discloses that hydrophilic 6-hydroxychoman compounds, which are used as the stabilizer Cyr, have anti-oxidant properties; see, e.g., col. 2, lines 21-24.

In order to establish obviousness under 35 U.S.C. §103, the prior art must contain both a suggestion of the claimed method and provide a reasonable expectation of success for such method; see, e.g., In re Vaeck, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); and In re Dow Chemical Co., 5 USPQ2d 1529 (Fed. Cir. 1988). Based on the above-discussed disclosures of Solanki and Cyr, it is strongly urged that one of ordinary skill in the art would not have had a reasonable expectation of success in using the weak oxidizing agents of Solanki to stabilize a radiopharmaceutical such as depreotide disclosed in Cyr. Although both references are in the same general field regarding stabilizing of

radiopharmaceuticals, they are each directed to stabilizing different types of radiopharmaceuticals using different types of agents for doing so. Solanki discloses using a weak oxidizing agent which is particularly selected to stabilize particular types of lipophilic radiopharmaceuticals, i.e., the propyleneamineoximes, mercaptoethyl triglycines, bisaminothiols, kethoxal bisthiosemicarbazones, ethyl cysteinate dimers and boronic acid adducts recited at col. 1, lines 20-49. Cyr discloses using an anti-oxidant agent to stabilize radiopharmaceuticals with particular emphasis on those having peptide-based targeting agents. Based on these teachings, one of ordinary skill in the art would have no reasonable expectation of success in using Solanki's weak oxidizing agent to stabilize the peptide-based radiopharmaceuticals of Cyr, such as depreotide. Solanki teaches one of ordinary skill in the art that the weak oxidizing agents taught as stabilizers therein were designed specifically for stabilizing the types of lipophilic radiopharmaceuticals disclosed at col. 1, lines 20-49, which do not include peptide-based radiopharmaceuticals. Solanki makes clear that its agents are specific to stabilizing these particular radiopharmaceuticals, thus, no reasonable expectation of their successful use with other radiopharmaceuticals is created. Cyr also fails to provide such reasonable expectation of success since it teaches to one of ordinary skill in the art the use of a different type of stabilizer to stabilize a peptide-based radiopharmaceutical. The fact that Solanki uses an oxidizing agent while Cyr uses an anti-oxidant – i.e., their apparent opposite activity – would actually create great doubt to one of ordinary skill in the art that one agent could successfully be used interchangeably to stabilize the radiopharmaceuticals taught in the other reference. Solanki even contrasts the undesired use of an antioxidant with their desired weak oxidizing agents; see, e.g., col. 6, lines 7-11. One of ordinary skill in the art would not have reasonably expected that an oxidizing effect stabilizer would be useful to stabilize a certain type of radiopharmaceutical when the art teaches that an anti-oxidant stabilizer is needed to stabilize that type of radiopharmaceutical.

Appellants urge that this is not a case where it would have been obvious to combine the compositions of Solanki and Cyr to form a third composition because they are used for the same purpose (see paragraph bridging pages 4-5 of the Final Office Action citing In re Kerkoven, 205 USPQ 1069 (CCPA 1980)). Kerkhoven is

distinguished because, in the instant case, the purposes of the Solanki and Cyr compositions are not the same. Solanki's purpose is to provide a weak oxidizing effect to stabilize certain types of lipophilic radiopharmaceuticals and Cyr's purpose is to provide an anti-oxidant effect to stabilize other types of radiopharmaceuticals, particularly ones with peptide complexing agents. Although both have the ultimate purpose of stabilizing a radiopharmaceutical, such purpose is achieved in distinct ways such that one of ordinary skill in the art would not expect interchangeability of the agents. The facts of Kerkoven are additionally distinguished because Kerhoven related to combining agents whereas the instant facts would require substituting one type of stabilizing agent for another type of stabilizing agent, not combining them.

For the above reasons alone, it is urged that there is not sufficient motivation to combine the reference teachings in the manner alleged to render the invention of the claims on appeal obvious to one of ordinary skill in the art. Thus, at least for this reason, it is believed that the rejection under 35 U.S.C. §103 is not supported on the record.

Appellants also urge that, even if combined, the reference teachings would not result in appellants' invention. The combination of Solanki with Cyr would additionally be distinct from appellants' invention in failing to disclose a composition or method containing "iodide ions or a compound which releases or generates iodide ions." Solanki discloses the use of a weak oxidizing agent as its stabilizer. Solanki's preferred agent is a sodium hypochlorite solution; see, e.g., the Abstract and col. 6, lines 10-27. Solanki, however, also mentions iodine as a possible weak oxidizing agent; see, col. 2, lines 5-7. Solanki makes no disclosure specific to the use of "iodide ions or a compound which releases or generates iodide ions" as the stabilizing agent.

The suggestion to use iodine as the oxidizing agent in Solanki is not equivalent to or suggestive of the use of iodide ions. The term "iodine" can be used to describe the element, I, but is clearly used in Solanki as describing the compound I_2. Note the distinction between the compound iodine and iodide ions in the excerpt from Concise Encyclopedia Chemistry (of record in this prosecution). Although iodide ions can be made from iodine under certain conditions, such conditions are not those used in Solanki; nor does Solanki provide any disclosure or motivation to suggest the use of conditions under which iodine provides iodide ions in its compositions. The fact that Solanki

separately discusses the use of iodide salts for use with the eluate (see following paragraph) makes clear that Solanki did not intend the term iodine to include iodide salts.

The disclosure at col. 7, line 31, to col. 8, line 50, of Solanki regarding the use of sodium iodide with the eluate does not teach or suggest the use of sodium iodide to stabilize the complex. Solanki does not teach or suggest here that sodium iodide is added to the Tc-99m HMPAO complex. Instead, it is only added to the Tc-99m pertechnetate eluate solution – before the radionuclide is combined with the complexing/targeting agent – to overcome the age restriction on the eluate. The eluate is the radioactive entity before it is complexed with a complexing agent. Solanki does not teach or suggest the addition of sodium iodide or any other iodide salt to the complex as a stabilizer for the complex.

Cyr teaches nothing remotely related to the use of iodide ions as stabilizers.

Thus, even if Solanki and Cyr were properly combinable, neither of them disclose the use of stabilizers containing iodide ions or a compound which releases or generates iodide ions. Nor does either reference disclose a method wherein iodide ions aid in stabilizing a radiopharmaceutical composition with a targeting agent against degradation, thus, maintaining high radiochemical purity of the composition. Accordingly, even assuming for argument, that it would have been obvious to interchange the stabilizers taught in Solanki and Cyr, such combination would still not meet or suggest the recited iodide ion element of the instant claims. In any event, for the reasons discussed above, one skilled in the art would not have been motivated to use the stabilizing agents of Solanki to stabilize the depreotide pharmaceutical of Cyr.

For the above reasons, it is urged that one of ordinary skill in the art would not be motivated to combine the prior art in a manner which would suggest appellants' invention and, even if combined, the prior art would not result in or suggest appellants' invention to one of ordinary skill in the art. Thus, the rejection under 35 U.S.C. §103 is not supported by the cited prior art and should be withdrawn.

1b. Claims 2 and 3 are not obvious to one of ordinary skill in the art from Solanki (U.S. Patent No. 5,262,175) in view of Cyr (U.S. Patent No. 6,881,396), and, thus, the rejection thereof under 35 U.S.C. §103 is not supported on the record.

Because claims 2 and 3, on appeal, are dependent on claim 1, on appeal, all the

arguments made above in part 1a. apply equally in traversal of the rejection of claims 2 and 3 and those arguments are incorporated by reference herein.

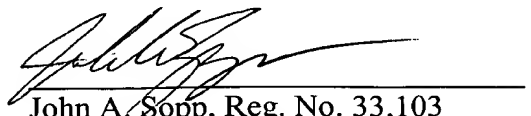
The inventions of claims 2 and 3, on appeal, are additionally distinguished from the combination of Solanki and Cyr (assuming for argument the propriety of their combination) because it is even more clear that Solanki and Cyr fail to disclose use of an iodide salt (claim 2) or alkali metal iodide salt (claim 3) to stabilize a radiopharmaceutical containing a radionuclide and a targeting agent. Although, for the reasons stated above, applicants urge that the references fail to suggest the use of iodine ions for stabilization, it is even more clear that they fail to suggest the use of an iodide salt or alkali metal iodide salt. For example, even if it were considered that Solanki's disclosure of the use of iodine as a weak oxidizing agent would provide iodine ions and that it would be obvious to use iodine to stabilize the radiopharmaceutical compositions of Cyr – both points being disputed above – such a conclusion would still not suggest to one of ordinary skill in the art the use of an iodide salt or alkali metal iodide salt for such stabilization.

Accordingly, it is urged that one of ordinary skill in the art would not be motivated to combine the prior art in a manner which would suggest the invention of appellants' claims 2 or 3, on appeal, and, even if combined, the prior art would not result in or suggest appellants' invention to one of ordinary skill in the art. Thus, the rejection of these claims on appeal under 35 U.S.C. §103 is further unsupported by the cited prior art and should be withdrawn.

For all of the above reasons, it is urged that the Final rejection of claims 1-4, 6, 8-10 and 32-33, on appeal, is in error and should be reversed.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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CLAIMS APPENDIX

1. A composition comprising:

- a radionuclide, excluding iodine radionuclides,
- a targeting agent, and
- iodide ions or a compound which releases or generates iodide ions,

where the iodide ions aid in stabilizing the composition against degradation thus maintaining high radiochemical purity of the composition, and,

where the targeting agent:

- is a peptide, oligonucleotide, antibody or peptidomimetic, or
- is a targeting agent bonded to a complexing moiety, of the following formula:

$A—CZ(B)—[C(R^1R^2)]_n—X$

wherein A is H, HOOC, H_2NOC, (peptide, oligonucleotide, or antibody)-NHOC, (peptide, oligonucleotide, or antibody)-OOC or R^4; B is H, SH or $—NHR^3$, $—N(R^3)$-(peptide, oligonucleotide, antibody or small organic compound) or R^4; X is SH or $—NHR^3$, $—N(R^3)$-(peptide, oligonucleotide, or antibody) or R^4; R^1, R^2, R^3 and R^4 are independently H or straight or branched chain or cyclic lower alkyl; n is 0, 1 or 2; and, Z is H, SH or R^4; provided that: (a) where B is $—NHR^3$ or $—N(R^3)$-(peptide, oligonucleotide, or antibody), X is SH and n is 1 or 2; (b) where X is $—NHR^3$ or $—N(R^3)$-(peptide, oligonucleotide, or antibody), B is SH and n is 1 or 2; (c) where B is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, or antibody)-NHOC, (peptide, oligonucleotide, or antibody)-OOC, X is SH and n is 0 or 1; (d) where A is H or R^4, then, where B is SH, X is $—NHR^3$ or $—N(R^3)$-(peptide, oligonucleotide, or antibody) and where X is SH, B is $—NHR^3$ or $—N(R^3)$-(peptide, oligonucleotide, or antibody); (e) where X is H or R^4, A is HOOC, H_2NOC, (peptide, oligonucleotide, or antibody)-NHOC, (peptide, oligonucleotide, or antibody)-OOC and B is SH; (f) where Z is methyl, X is methyl, A is HOOC, H_2NOC, (peptide, oligonucleotide, or antibody)-NHOC, (peptide, oligonucleotide, or antibody)-OOC and B is SH and n is 0; and (g) where Z is SH and X is SH, n is not 0; and wherein the thiol moiety is in the reduced form and the complexing group is capable of being covalently linked to the peptide, oligonucleotide, or antibody.

2. The composition of claim 1, wherein the iodide ions are provided by an iodide salt in the composition.

3. The composition of claim 1, wherein the iodide ions are provided by an alkali metal iodide salt in the composition.

4. The composition of claim 1, wherein the radionuclide is associated with a targeting agent.

6. The composition of claim 4, wherein the targeting agent is associated with the radionuclide by being bonded to a complexing moiety which complexes the radionuclide.

8. The composition of claim 4, wherein the targeting agent is a somatostatin receptor binding peptide.

9. The composition of claim 8, wherein the somatostatin receptor binding peptide is depreotide or P2045.

10. The composition of claim 1, wherein the radionuclide is Tc-99m.

32. A composition comprising:

- a Tc-99m radionuclide,
- a depreotide or P2045 targeting agent, and
- iodide ions or a compound which releases or generates iodide ions,

where the iodide ions aid in stabilizing the composition against degradation thus maintaining high radiochemical purity of the composition.

33. The composition of claim 1, wherein the radionuclide is Tc-99m, Re-188, Re-186, Ga-67, In-111, Yb-169, H-3, C-14, N-15, F-18, P-32, P-33 or Y-90.

EVIDENCE APPENDIX

1. Concise Encyclopedia Chemistry, pub. Walter de Gruyter 1994 (copy attached). First cited in Applicants' Reply filed December 8, 2005, and implicitly acknowledged and considered in the Final Office Action of March 14, 2006 (page 5, second and third full paragraphs).

RELATED PROCEEDINGS APPENDIX

(None)

Concise Encyclopedia Chemistry

Translated and revised by
Mary Eagleson

Walter de Gruyter Berlin · New York 1994

and preservatives, e.g. in eye medications. They have antibiotic activity against a large number of bacteria; gram-positive bacteria are particularly susceptible. In addition, I. act as antimycotics and can inactivate viruses. Some examples are benzododecinium bromide, alkonium bromide and cetylpyridinium chloride.

Invert sugar: an equimolar mixture of D-glucose and D-fructose. I. is obtained by acid-catalysed hydrolysis of sucrose. Because fructose is highly levorotatory, the sign of the optical rotation of the solution changes during the course of the hydrolysis, i.e. an inversion occurs. I. is present in honey at about 70% concentration. It is used to make artificial honey and to keep foods moist.

In vitro: (Latin, meaning "in glass") an adjective applied to experiments done under artificial conditions, e.g. in a test tube.

In vivo: (Latin, meaning "in life") an adjective applied to experiments in a living cell or organism.

Iodate: a salt of iodic acid, HIO_3, with the general formula MIO_3. I. are more stable than chlorates or bromates, but like these compounds, they are strong oxidizing agents. When mixed with combustible substances, I. explode easily on impact. Alkali iodates are obtained by dissolving iodine in hot alkali hydroxide solutions, or by anodic oxidation of alkaline iodide solutions. The slight amounts of sodium and calcium iodates found in Chile saltpeter are an important starting material for production of iodine.

Iodic acid: HIO_3, transparent, colorless, rhombic crystals; M_r 175.93, density 4.650, m.p. 110 °C. I. is very soluble in water and is a medium strong acid (pK 0.804); it is a strong oxidizing agent and is the only halogen(V) acid of the type HXO_3 which can be isolated in anhydrous form. I. is obtained by oxidation of iodine with strong oxidizing agents such as conc. nitric acid, hydrogen peroxide, ozone or chlorine. If the oxidation is done with chlorine, hydrochloric acid is formed simultaneously: $I_2 + 5\ Cl_2 + 6\ H_2O \rightarrow 2\ HIO_3 + 10\ HCl$; the HCl must be removed by addition of silver oxide to pull the equilibrium toward the products. I. can be released from iodates by reaction with sulfuric acid: $MIO_3 + H_2SO_4 \rightarrow HIO_3 + MHSO_4$.

Iodides: metal salts of hydroiodic acid, and also covalent compounds of iodine with nonmetals, including organic compounds such as alkyl or aryl iodides. Alkali and alkaline earth metals form ionic, water-soluble I., MI or MI_2, while a few heavy-metal iodides are insoluble in water, e.g. silver(I) iodide, AgI (yellow), copper(I) iodide, CuI (colorless), mercury(II) iodide, HgI_2 (red) and thallium(I) iodide, TlI (yellow). There are also covalent, hydrolysable I., including phosphorus(III) iodide, PI_3, and silicon(IV) iodide, SiI_4.

Iodination: see Halogenation.

Iodine, symbol *I*: an element in group VIIa of the periodic system, the Halogens (see); a nonmetal, with only one natural isotope, Z 53, atomic mass 126.9045, valence - I, +I, +III, +IV, +V, +VII, density 4.942, m.p. 113.6 °C, b.p. 185.24 °C, standard electrode potential (I^-/I_2) +0.5255 V.

Properties. I forms gray-black, semiconducting, rhombic crystals with a metallic sheen; even at room temperature they are somewhat volatile, forming a vapor of violet I_2 molecules. If I is heated fairly slowly, it will completely sublime below the melting point. It has a characteristic pungent odor, and the vapors are poisonous. Solid I forms a layered lattice, in which the intermolecular distance between the atoms of neighboring I_2 molecules is 349.6. This is a very short distance, and delocalization of electrons within the layers leads to two-dimensional semiconductor properties and the metal-like sheen of I. In nonpolar solvents, such as carbon disulfide, chloroform or tetrachloromethane, I. dissolves as molecules, giving a violet solution. On the other hand, the red solutions of I. in aromatic hydrocarbons and the brown solutions in donor solvents such as diethyl ether, acetone, dioxane and pyridine, contain charge-transfer complexes of the I. with the solvent molecules, $I_2 \cdot D$. I. is only very slightly soluble in water (0.022 g in 100 g H_2O), and gives a weak, brownish yellow color. However, it dissolves very readily in potassium iodide solution, forming dark brown potassium triiodide, KI_3. I. is chemically very similar to the other halogens, but its reactions are less vigorous. It reacts vigorously with a number of elements, including iron, mercury, sulfur, phosphorus, antimony, silicon and nickel, forming iodides. A characteristic of I. is its ability to form cationic compounds in the +1 and +3 oxidation states. For example, iodine(I) perchlorate is can be made by reaction of I. with silver perchlorate in a benzene solution: $I_2 + AgClO_4 \rightarrow IClO_4 + AgI$; iodine(III) perchlorate is obtained by reaction of the same substances in ether at - 85 °C: $2\ I_2 + 3\ AgClO_4 \rightarrow I(ClO_4)_3 + 3\ AgI$. Iodine(I) compounds can be stabilized by Lewis bases, e.g. $[IPy_2][ClO_4]$ and $[Ipy_2][NO_3]$.

Analysis. I is characterized by formation of an intense blue inclusion compound with starch (see Iodometry). The iodide ion, I^-, can be detected by reaction with silver nitrate to form yellow silver(I) iodide, AgI. Iodine also forms a dark red mercury(II) iodide, HgI_2, and yellow lead(II) iodide, PbI_2. Elemental I. can be determined quantitatively by titration with sodium thiosulfate, while iodide is determined by argentometry or gravimetrically as AgI.

Occurrence. I makes up $6.1 \cdot 10^{-5}$% of the earth's crust, and is thus one of the least abundant elements. It is found only as its compounds in nature; the most important iodine deposits are the saltpeter deposits in Chile, and natural waters (from deep wells and brines from petroleum and natural gas wells). Chile saltpeter can contain up to 0.3% I in the form of sodium iodate, $NaIO_3$, or calcium iodate (lauterite), $Ca(IO_3)_2$. Water from deep layers used for I. production contain up to 50 ppm I.; the brines from petroleum deposits can contain up to 100 ppm. I. also occurs widely in rocks and soils (about 5 ppm). Seawater contains about 0.002% I., mainly in organic form. Various marine organisms, such as kelp and algae, corals and sponges can enrich I. up to 0.45% of their dry matter.

I. is an important bioelement; plants contain about 0.1 ppm. It is essential for the human body, as it is a component of the thyroid hormones thyroxin and triiodothyronin. The daily human requirement is about 2 mg. I deficiency leads to goiter, and in severe cases, to cretinism.

Production. I. is enriched in the mother liquors

s. If I is heated fairly
olime below the melting
pungent odor, and the
I forms a layered lattice,
r distance between the
ecules is 349.6. This is a
localization of electrons
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solution. On the other
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$)_4$ + AgI; iodine(III) per-
ction of the same substan-
+ 3 $AgClO_4 \rightarrow I(ClO_4)_3$ +
nds can be stabilized by
O_4] and $[Ipy_2][NO_3]$.
:ed by formation of an in-
ıpound with starch (see
n, I^-, can be detected by
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rms a dark red mercury(II)
lead(II) iodide, PbI_2. Ele-
ıed quantitatively by titra-
ate, while iodide is deter-
gravimetrically as AgI.
$6.1 \cdot 10^{-5}$% of the earth's
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pounds in nature; the most
are the saltpeter deposits in
(from deep wells and brines
ral gas wells). Chile saltpe-
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lcium iodate (lauterite),
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ım I.; the brines from pe-
tain up to 100 ppm. I. also
d soils (about 5 ppm). Sea-
002% I., mainly in organic
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can enrich I. up to 0.45% of

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ır the human body, as it is a
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ily human requirement is
ıeads to goiter, and in severe

ched in the mother liquors from processing Chile saltpeter. The iodate present in the liquor is reduced with sulfurous acid to I: 2 HIO_3 + 5 $H_2SO_3 \rightarrow I_2$ + 5 H_2SO_4 + H_2O. The precipitated I. is filtered out and purified by multiple sublimation steps. To obtain I from iodide-containing waters, it is first oxidized with chlorine to I_2, then isolated and purified by repeated absorption and desorption, reduction and oxidation steps. A small amount of I. is still isolated from seaweed.

Application. I. is used as an antiseptic and to stop bleeding (see Iodine, tincture of). Considerable amounts of I. are used in the synthesis of drugs used to treat abnormal thyroid function. Iodides are added to animal feeds as trace element sources. I. and its compounds are used in photochemistry, preparative and analytical chemistry, and organoiodine compounds are used as x-ray contrast media. The nuclide ^{131}I is obtained from nuclear reactors; it is a β-emitter with a half-life of 8.04 d and is used in medicine.

Historical. I. was first isolated from the ashes of seaweed in 1811 by Coutois. In 1815, Gay-Lussac demonstrated that it is an element, and it was named after the color of its vapor (the Greek word "ioedides" means "violet").

Iodine azide: see Halogen azides.

Iodine bromide: see Iodine halides, see Interhalogen compounds.

Iodine chlorides: see Iodine halides, see Interhalogen compounds.

Iodine charcoal: granulated activated charcoal containing iodine. It is used to pick up spilled mercury.

Iodine cinnabar: see Mercury iodides.

Iodine fluorides: see Iodine halides, see Interhalogen compounds.

Iodine halides: very reactive Interhalogen compounds (see) obtained by reaction of iodine with the lighter halogens. The I. have general formulas IX (X = F, Cl, Br), IF_n (n = 3, 5, 7) and $(ICl_3)_2$. ***Iodine monofluoride***, IF, is a chocolate-brown solid, dec. above 0°C; ***iodine monochloride***, ICl, is a dimorphous compound. α-ICl forms ruby-red needles, m.p. +27.38°C, and β-ICl (metastable) forms red-brown, rhombic platelets, m.p. 13.9°C, b.p. 97.4°C. ***Iodine monobromide***, IBr, forms red-brown crystals, m.p. +41°C, b.p. +116°C, and ***iodine trifluoride***, IF_3, is a yellow powder (at -78°C); m.p. -28°C (dec.). ***Iodine trichloride*** $(ICl_3)_2$ forms yellow crystalline needles, m.p. 101°C (at 1.6 MPa), b.p. 77°C (dec.). ***Iodine pentafluoride***, IF_5, is a colorless liquid, m.p. +9.42°C, b.p. 104.48°C; ***iodine heptafluoride***, IF_7, colorless gas, m.p. +6.45°C, b.p. 4.77°C.

Iodine number: see Fats and fatty oils.

Iodine oxides: ***Diiodine tetroxide***: I_2O_4, yellow, grainy compound, M_r 317.81, density 4.2, m.p. 130°C. When heated to about 135°C, it undergoes a disproportionation reaction: 5 $I_2O_4 \rightarrow$ 4 I_2O_5 + I_2. I_2O_4 reacts with alkali hydroxide solutions to form iodide and iodate. It is synthesized by a slow reaction of hot, concentrated sulfuric acid with iodic acid. Structurally, I_2O_4 is probably iodosyl(III) iodate(V). ***Diiodine pentoxide, iodine(V) oxide***: I_2O_5, white, crystalline powder, M_r 333.80, density 4.799, m.p. ≈ 300°C (dec.). When heated to about 300°C it decomposes into the elements. It can be considered the anhydride of iodic acid, with the structure O_2IOIO_2 (∢IOI 139.2°, terminal I-O distances, 180 pm, bridge IO distance, 194 pm): I_2O_5 + $H_2O \rightleftharpoons$ 2 HIO_3. I_2O_5 is obtained by heating iodic acid to about 250°C; it is the only exothermal halogen oxide.

Diiodine heptoxide, iodine(VII) oxide, I_2O_7, an orange, polymeric solid, M_r 365.81, formed by dehydration of periodic acid with concentrated sulfuric acid. When heated to 100°C, it is converted to I_2O_5 according to the equation $I_2O_7 \rightarrow I_2O_5 + O_2$.

Iodine red: see Mercury iodides.

Iodine spirits: a dark, red-brown liquid which smells like iodine; it is made by dissolving certain amounts of iodine and potassium iodide in 80% ethanol. I. is used to disinfect wounds, but because of possible allergic reactions, it is now rarely used.

Iodine, tincture of: a dark brown liquid which smells like iodine; density 0.898 to 0.902. I. is an alcohol solution of iodine which contains 7% iodine and 3% potassium iodide; it is used in medicine to disinfect wounds.

Iodoacetic acid: I-CH_2-COOH, a colorless, crystalline compound; m.p. 83°C. I. is soluble in water and alcohol. It can cause severe burns on the skin. It is synthesized by reaction of chloroacetic acid with potassium iodide in aqueous solution. It is used in organic syntheses and in biochemistry to inhibit certain enzymes.

Iodobenzene, ***phenyl iodide***: C_6H_5-I, a colorless liquid which turns brown in the air, due to precipitation of iodine; m.p. -31.3°C, b.p. 188.3°C, n_D^{20} 1.6200. I. is barely soluble in water, but dissolves readily in alcohol, ether, acetone and benzene. It can be made by iodination of benzene in the presence of nitric acid or by the Sandmeyer reaction (see) from benzene diazonium salts. I. is used in the synthesis of iodine-containing x-ray contrast materials.

Iodoform, ***triiodomethane***: CHI_3, forms yellow, hexagonal platelets with a penetrating, sweetish odor; m.p. 123°C, b.p. about 218°C. I. is practically insoluble in water, but is soluble in ether, acetone, carbon disulfide and chloroform. It is steam volatile. It decomposes readily in the presence of light. I. can be synthesized by the Iodoform test (see); industrially, it is made by electrolysis of alkali iodides in alcohol-water or acetone-water mixtures. I. is sometimes still used as an antiseptic for treating cuts, and as a non-sulfur vulcanizing material for rubber.

Iodoform test: a reaction used to detect the presence of an acetyl group, CH_3-CO- (e.g. in acetone) or a 1-hydroxyethyl group, CH_3-CH(OH)- (e.g. in ethanol). Iodine and potassium hydroxide react with these functional groups to form iodoform, which is a yellow, water-insoluble compound. For example: CH_3-CH(OH)-R + I_2 + 2 KOH → CH_3-CO-R + 2 KI + 2 H_2O; CH_3-CO-R + 3 I_2 + 3 KOH → CI_3-CO-R + 3 KI + 3 H_2O; CI_3-CO-R + KOH → HCI_3 + R-COOK. The I. can be used with compounds which are fairly insoluble in water in the presence of a solubilizer such as dioxane. This reaction is a variant of the Haloform reaction (see).

Iodomethane: same as Methyl iodide (see).

Iodometry: method of redox analysis based on the corresponding redox pair iodine/iodide. With a standard potential E_0 = +0.536, iodide is a weak oxidizing agent. Strong reducing agents, e.g. tin(II), arsenic(III), thiosulfate, sulfide and sulfite, can be ti-